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Original Article

Does magnesium sulfate delay the active phase of labor in women with premature rupture of membranes? A randomized controlled trial

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ABSTRACT

Objective: Administration of many drugs including magnesium sulfate (MS) has considerable influences on pregnancy outcomes. The present study investigates the effects of MS administration on reaching the active phase of labor in women with premature rupture of membrane (PROM) and subsequent fetal complications.
Materials and methods: A double blind, randomized, placebo-controlled trial was performed among primipara women referred to the PROM center in Tehran, Iran between March 2010 and August 2012. Patients were equally allocated into two groups; the intervention group who received MS ($n = 46$) and the control (placebo) group ($n = 46$). Both groups received a corticosteroid, 1g oral azithromycin (oral) and 2 g ampicillin (IV) every 6 hours for 48 hours, followed by amoxicillin (500 mg orally 3 times daily) for an additional 5 days. None of the research staff were aware of the treatment allocation of patients in order for blinding purposes.
Results: Administration of MS in intervention group increases this period 2.7 times compared to the control group. In women whose gestational age was <30 weeks, MS administration increased the active phase of labor up to 77%. Administration of magnesium sulfate reduced the risk of respiratory distress syndrome significantly ($p = 0.002$), without producing any adverse pregnancy outcomes.
Conclusion: Magnesium sulfate increases delay in reaching the active phase of labor in mothers with PROM, without producing adverse birth outcomes. (Registration ID in IRCT; IRCT2012091810876N1).

Introduction

Preterm labor refers to progressive cervical dilatation or effacement associated with regular uterine contractions (≤6/hour) [1]. It is an imperative factor in infant deaths and the second cause of infant mortality followed by congenital anomalies [2,3]. Prematurity or gestational age <37 weeks is an essential health indicator for all communities. Unfortunately despite progress made in identifying causes of preterm labor, it has increased in recent years [2,4].

Abortion, history of cesarean section, and preeclampsia are reported to be the significant causes of preterm labor [5]. Different treatment methods have been evaluated to prevent preterm birth, all of which have been used to delay preterm labor and reduce fetal complications [6]. Pharmacological inhibition of premature uterine contractions is among the widely available methods, but there is still discrepancy regarding the treatment of choice [7–9].

Magnesium sulfate, prostaglandin inhibitors, calcium channel blockers, and nitric oxide-releasing drugs have shown positive effects on preterm birth [10]. The use of tocolytics such as magnesium sulfate is one of the regular treatments to prevent preterm labor. However, there is little published clinical evidence on its beneficial

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effects [11,12]. Tocolytics are used to delay the active phase of labor for at least 48 hours [13]. Generally there is a little controversial information regarding utility of MS in case of premature rupture of membrane (PROM). A meta-analysis in 2009 showed that MS administration is not able to reduce the frequency of deliveries within 48 hours, 7 days, or early–late preterm birth. The authors concluded that no other tocolytic class resulted in improved newborn outcomes when compared with MS tocolysis and it is suitable to hold back MS tocolysis from women with recurrent preterm labor afterwards [14].

The present randomized control trial aimed to investigate the effects of magnesium sulfate on delay in reaching the active phase of labor in women with PROM and subsequent fetal complications in the Iranian population.

Materials and methods

It was a randomized control trial conducted in the Mahdieh Medical Centre, Tehran, Iran between March 2010 and August 2012.

Inclusion criteria were: (1) pregnant women with gestational age < 34 weeks who were hospitalized for premature rupture and labor complaints; (2) the absence of concomitant disease such as chorioamnionitis or a history of drug sensitivity to magnesium sulfate; (3) no previous use of magnesium sulfate in order to curb labor complaint in a recent pregnancy; and (4) the absence of twin or multiple pregnancy. Exclusion criteria were: (1) probable case of chorioamnionitis; (2) progress of labor as 4 cm cervical dilatation; (3) allergy or medical complications in combination with magnesium sulfate; (4) fatal fetal anomalies; (5) nonreassuring fetal status; (6) severe fetal growth restriction; (7); severe preeclampsia or eclampsia; and (8) maternal hemorrhage with hemodynamic instability. Cases and controls were matched in terms of expecting their first child, maternal age, gestational age (weeks), and a history of abortion. Study population included all women expecting their first child and referred to the Center with preterm PROM. Patients were allocated into two groups; intervention (magnesium sulfate, $n = 46$) and control (placebo, $n = 46$).

According to inclusion criteria, duration of study, and the type of research design in which random allocation was used as a mechanism for control of known and unknown confounding variables, matching was based on mentioned factors and other variables were ignored.

In this study, premature rupture was defined as fetal membrane rupture prior to 34 weeks of gestational age. Tocolytic medication referred to those drugs which inhibit uterine contractions. Preterm labor referred to persistent uterine contractions (e.g., at least 4 every 20 minutes or 8 every 60 minutes) with premature rupture of membranes or cervical dilation of 1–3 cm or effacement exceeding 50% or a change in cervical dilation or effacement detected by serial examinations.

For calculation of sample size, the Gehan and similar studies were used considering a maximum of 5% error and 80% power [15,16]. After determining sample size and statistical population, 92 patients were selected randomly from women expecting their first child who had been referred to Mahdieh Hospital, Tehran, Iran. For random allocation, treatment diets (intervention and control groups) were packed in separate packages and coded from 1 to 92 by an expert midwife. When an eligible patient was accepted into the study, another expert interviewed her and a code from 1 to 92 was assigned to questionnaires regardless of medicinal packages coding. Finally, those who had an odd code were allocated to the intervention group and others to the control group.

Placebo used in this study was prepared by the School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. None of the research staff were aware of the treatment allocation of patients in order for blinding purposes. In the intervention group, patients received 4 g of magnesium sulfate dissolved in 100 mL of normal saline solution for 20 minutes to reach loading dose. Then, they received 2 g of magnesium sulfate dissolved in 100 mL of normal saline by infusion every hour. Infusion was continued until 24 hours after complete cessation of uterine contractions [17]. All steps were considered blinding principles in the control group too. Both groups received a corticosteroid, 1g of oral azithromycin and ampicillin 2 g intravenously every 6 hours for 48 hours, followed byamoxicillin (500 mg orally 3 times daily) for an additional 5 days. During treatment, regular examination was done hourly to measure respiratory and urinary volume, Glasgow Coma Scale (GCS), Deep Tendon Reflex (DTR), fetal and maternal tachycardia, body temperature, and malodorous vaginal discharge to avoid fetal and maternal complications and consequences.

Data collection tool included a questionnaire which was completed by two trained midwives. This questionnaire contained information on maternal age, gestation weeks, pregnancy gravidity, having or not having a birth within 48 hours after drug administration, fetal and maternal complications, and birth weight.

Prior to entering the study, all patients were informed and consented to participate in the research. They were also allowed to be excluded from the research whenever they wished.

Data description was done using descriptive statistics including mean, standard deviation, variance, and frequency distribution tables. The impact of medication on delay time was determined by analytical statistics including Student t test, Mann–Whitney, and regression analysis. All analyses were conducted using SPSS software version 20 (SPSS Inc.,Chicago, IL, USA).

This research was approved by the Ethics Committee in the Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Results

In this study two groups including 46 patients receiving magnesium sulfate (intervention) and 46 patients receiving placebo (control) were used to determine the effects of medication on delay in the active phase of labor and fetal complications. Mean age and standard deviations was 26.9 ± 3.5 years. The majority of patients (74.2%) had academic levels of education. There was no significant difference between cases and controls in terms of education levels ($p = 0.76$). In terms of employment, 14% of patients were clerks, 24% service workers and shop keepers, 11% professionals, 19% in elementary occupations, and the rest (32%) were housewives. Table 1 represents basic characteristics of the two groups prior to intervention. There was no significant statistical difference in basic characteristics between the two groups. Moreover, according to linear and logistic regression analyses, with matching patient's age and her gestational age, only magnesium sulfate was effective in the delay of the active phase of labor (Table 2). The administration of magnesium sulfate in women with preterm labor pain leads to inhibition of uterine contractions and delay in delivery for at least 48 hours. Administration of magnesium sulfate in the intervention group increases this period 2.7 times the same as in the control group. In women with gestational age <30 weeks, magnesium

Table 1
Characteristics of intervention and control groups.

Variable	Groups	Mean ± SD	p
Age (y)	Intervention	26.85 ± 5.1	0.92
	Control	26.96 ± 5.7	
Gestational age (wk)	Intervention	30.94 ± 1.77	0.12
	Control	31.54 ± 1.8	
History of abortion (%)	Intervention	26.1	0.31
	Control	17.4	

Table 2
Effects of magnesium sulfate and placebo on delay of the active phase of labor.

Group	Variable	Linear regression[a]		Logistic regression[b]	
		SC	95% CI	AOR	95% CI
Intervention	Age (y)	0.119	−1.4–3.4	0.95	0.86–1.4
	Gestational age (wk)	−0.07	−1.83–0.92	1.25	0.95–1.6
	Magnesium sulfate (yes/no)	0.631	0.32–1.8	7.2	2.25–10.1
	History of abortion (yes/no)	0.13	−1.7–5.4	0.89	0.28–2.8
Control	Age (y)	0.6	−0.8–2.2	0.88	0.8–2.1
	Gestational age (wk)	−0.11	−0.7–1.1	1.1	0.7–1.7
	Placebo (yes/no)	0.161	−0.5–1.5	2.2	0.8–3.4
	History of abortion (yes/no)	0.11	−1.2–4.4	0.44	0.7–1.8

AOR = adjusted odds ratio; CI = confidence interval; SC = standardized coefficient.
[a] Delay time in continuous scale as dependent variable.
[b] Delay time in categorical scale as dependent variable.

Table 3
Demographic information of two groups of quantitative and qualitative variables.

Variable, mean ± SD or *n* (%)	Intervention	Control	*p*
Age of mother (y)	26.85 ± 5.13	26.99 ± 5.6	0.92
Gestational age (wk)	30.95 ± 1.78	31.54 ± 1.78	0.12
Latency (h)	114.1 ± 39.2	20.9 ± 18.8	>0.001
1st min Apgar	8.17 ± 1.39	8.04 ± 1.35	0.64
5th min Apgar	9.22 ± 1.6	9.22 ± 1	0.98
Birth weight (g)	1688.7 ± 560	1828 ± 541	0.23
History of abortion (yes/no)	12 (26.1)	8 (17.4)	0.31
RDS	14 (30.4)	29 (63)	0.002
Need NICU	32 (96.6)	34 (73.9)	0.64
IVH2	2 (4.3)	3 (6.5)	0.64
Infant death	1 (2.2)	3 (6.5)	0.30
Sepsis	5 (10.9)	8 (17.4)	0.37
Uterine atony	2 (4.3)	0 (0)	0.11
Chorioamnionitis	0 (0)	0 (0)	–

IVH2 = intraventricular hemorrhage; NICU = neonatal intensive care unit; RDS = respiratory distress syndrome.

sulfate leads to 77% increase in the active phase of labor. This time change has been 87.7% and 72.7% in women with 30–31 weeks and 32–33 weeks of gestational age (Table 3).

Administration of magnesium sulfate not only did not lead to adverse pregnancy outcomes, but also had positive effects in reducing respiratory distress syndrome ($p = 0.002$). Considering the impact of mentioned variables on fetal complications, logistic regression results showed that administration of magnesium sulfate has no effects on fetal complications (Table 4).

The weight variable has a positive effect at birth and prevents sepsis, so that every unit increase in weight will decrease the chances of infection by 0.3%. Regarding respiratory distress syndrome (RDS) outcome, it should be mentioned that the only effective variable is administration of magnesium sulfate which shows a strong protective effect. As a result, the chance of respiratory distress syndrome in infants who had received magnesium sulfate was 80% less than those who had received placebo. By every unit increase of gestational age, the probability to need care in neonatal intensive care unit (NICU) was decreased by 33%.

Discussion

Magnesium sulfate is an effective blocker in women with premature rupture to delay reaching the active phase of labor. In this study, all patients were matched in basic characteristics including age, gestational age, history of abortion, and educational level, so the results are less influenced by patients' characteristics. Mothers at gestational age between 16 weeks and 36 weeks are at greater risk for having premature pregnancies. This risk increases with less gestational age and having a history of more premature pregnancies [18]. In recent years, efforts have been made to provide better treatment strategies.

The regression analyses with regard to maternal age, gestational age, and a history of abortion showed that the administration of magnesium sulfate leads to at least 48 hours delay in the active phase of labor (OR = 27, 95% CI = 45.5–1.10). These findings indicate that the chance of delay in reaching the active phase of labor for those who have received magnesium sulfate was 2.7 times higher than the corresponding conditions for the control group. Other studies have confirmed the effects of magnesium sulfate on delay in reaching the active phase of labor [13,19]. Consumption of magnesium sulfate in women with gestational age <33 weeks has led to 77% increase in the active phase of labor (Fig. 1). However, in Agudelo overview which has been done on six clinical trials, the results indicate a significant reduction of cerebral palsy (OR = 0.69, CI = 0.55–0.88) following the consumption of magnesium sulfate [20], whereas it is known as a strong risk factor in the Mittendorf study. Moreover, this study states that the drug leads to more fetal complications [7] even though, preterm delivery itself is a risk factor and is associated with the choice of treatment, gestational age, and maternal age [21].

Many studies have been conducted regarding other outcomes associated with preterm delivery in the presence or absence of preterm premature rupture. For example, a study showed that the use of magnesium sulfate had reduced the risk of death in premature infants [22], but in the next study it had increased this risk [23]. Other studies have shown no significant difference in chorioamnionitis, birth weight, and frequency of days hospitalized in

Table 4
Effects of variables on neonatal outcomes.

Variable	Neonatal outcomes (OR, 95% CI)				
	Death	Sepsis	RDS	IVH	NICU
Age of mother (y)	1.41 (0.7 ± 2.2)	0.9 (0.75–1.1)	1.03 (0.94–1.12)	0.87 (0.68–1/11)	1.07 (0.93–1.2)
Gestational age (wk)	0.8 (0.4–1.6)	1.02 (0.92–1.13)	1 (0.95–1.06)	0.9 (0.8–1.3)	0.67 (0.53–0.84)
Latency (h)	1.18 (0.9–1.32)	0.99 (0.97–1.01)	0.98 (0.7–1.2)	1.004 (0.99–1.02)	0.99 (0.98–1)
1st min Apgar	0.7 (0.4–1.4)	1/14 (0.18–6.9)	0.41 (0.14–1.16)	1.18 (0.5–2.1)	0.8 (0.67–1.2)
5th min Apgar	0.9 (0.6–1.8)	1.65 (0.2–4)	2.67 (0.87–3.24)	1.18 (0.11–1.91)	0.78 (0.54–1.05)
Birth weight (g)	0.9 (0.62–1.17)	0.97 (0.95–0.99)	0.99 (0.98–1.1)	0.99 (0.98–1.02)	1 (0.99–1.02)
History of abortion (yes/no)	1.008 (0.7–1.46)	0.26 (0.04–1.1)	0.79 (0.25–2.5)	1.02 (0.3–1.41)	0.64 (0.2–3.9)
Administration of MS (yes/no)	2.23 (0.8–3.26)	4.54 (0.8–6.7)	0.21 (0.08–0.6)	3.2 (0.4–4.8)	2.69 (0.54–5.21)

CI = confidence interval; IVH = intraventicular hemorrhage; MS = magnesium sulfate; NICU = neonatal intensive care unit; OR = odds ratio; RDS = respiratory distress syndrome.

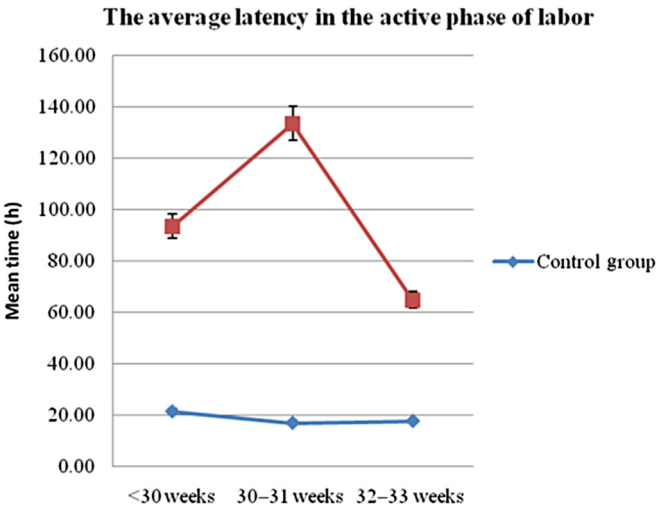

Fig. 1. Mean latency changes in the active phase of labor.

neonatal intensive care units, number of days supported by ventilator, sepsis, mortality, hyaline membrane disease, necrotizing enterocolitis, and intraventricular hemorrhage. There was no improvement in prenatal prognosis [24].

In this study, fetal respiratory distress, requiring care in neonatal intensive care unit (NICU), cerebral intra-ventricular hemorrhage, infant death, and sepsis were considered as fetal outcomes. According to results, magnesium sulfate did not have any effects on mentioned outcomes except RDS. The results of the present study on the outcome of death are consistent with other studies [20]. Logistic regression results showed that birth weight does not have protective effects to prevent sepsis, so that each unit increase in weight reduces the chance of infection by 0.3%. Moreover, those who had received magnesium sulfate had an 80% lesser chance of RDS risk. There was no case of chorioamnionitis and adverse effects of magnesium sulfate (Table 4). Given that risk factors for preterm delivery and response to treatment, complications, and infant and maternal mortality are different according to race and ethnicity, decisions on requiring treatment and preventing preterm delivery should be made separately based on each region's race, ethnicity, medical facilities, care centers for infants, and NICUs. However, the present study has tried to show real effects of magnesium sulfate in an Iranian community. In this research, magnesium sulfate increased the delay in reaching the active phase in mothers with PROM and there was no evidence of adverse fetal outcomes. However, due to different results and various studies, there was no firm decision on use or nonuse of this drug to prevent adverse fetal outcomes. Larger studies should be done with a focus on occurrence of fetal complications in women with preterm labor.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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